REMARKS

Claims 14, 16 and 22-38 are currently pending and stand rejected. Claims 14 and 16 are amended, claims 22-38 are cancelled and claims 39-48 are added herein.

Support for the present claim amendments and additions can be found throughout the specification and claims as originally filed. For example, support for new claim 39 can be found, *inter alia*, at page 2, lines 1-6; page 4, lines 4-30; page 6, line 28 to page 7, line 15; original claims 3 and 9. Support for new claims 40 and 41 can be found, *inter alia*, at page 4, lines 4-6; original claims 4 and 10. Support for new claim 42 can be found, *inter alia*, at page 4, lines 4-8; page 6, lines 21-23. Support for new claim 43 can be found, *inter alia*, at page 6, lines 23-26; original claim 12. Support for new claims 44-46 can be found, *inter alia*, at page 4, lines 19-25; original claims 5, 7 and 11. Support for new claims 47-48 can be found, *inter alia*, at page 4, lines 3-30; page 6, line 28 to page 7, line 15. No new matter is added and entry is respectfully requested.

Examiner Interview

Applicants greatly appreciate the thoughtful consideration shown their undersigned representative and patent counsel for assignee in an interview on 18 December 2003. The substance of the interview is hereby made of record as directed by MPEP § 713.04. The interview of 18 December 2003 took place between Examiner Dong Jiang, Primary Examiner Lorraine Spector, together with Peng Chen and David Devernoe (agents of the assignee). New Matter, anticipation and obviousness issues were discussed as they relate to claims 14, 16 and 22-38. Proposed claim amendments were provided. Agreement was reached regarding the non-applicability of *Takasu* as an anticipatory reference versus the present claims. It is also the Applicant's agents' understanding that an agreement was reached regarding the new matter rejection, as it was determined that claim 14 is directed to an adequately described species of the present invention.

Although an agreement was not reached with regard to the remaining anticipation rejection and the obviousness rejection, the Office invited the Applicant's agents to place their arguments on the record for full consideration. Further to this, the Office invited the Applicant's agents to restructure the claims such that they meaningfully incorporate the specific biological activity of the

compositions utilized in the present methods, to aid in further differentiating these claims from the cited references.

Withdrawal of Objections and Rejections

The Applicant acknowledges, with appreciation, the Office's indication that the enablement rejection of claims 30-33 and the anticipation rejection of claims 14 and 16 (over Fukuda, EP 0528271) are withdrawn in light of the Amendment of 30 July 2003.

New Matter Rejection

Prior to the agreement reached at the interview of 18 December 2003, claim 14 stood rejected on the basis that it introduced new matter that was purportedly not described in the specification as filed. Notwithstanding the agreement on the issue, out of the concern to provide a complete reply to the 6 November 2003 Office Action, the Applicant herein places the thrust of his argument on the record for reference by the Office.

The Applicant asserts that claim 14 is adequately supported by the specification and claims as filed. *See, e.g.*, page 1, lines 8-12; page 4, lines 4-13; page 5, lines 23-26; sequence listing. The claimed PTH antagonist falls within the original claimed range of a PTH antagonist having an N-terminal position starting at any position spanning from position 2 through position 34 of SEQ ID NO:1 (PTH_{1-84}). Position 8 clearly falls within this range. The descriptive language supporting the claimed PTH antagonist composition means the same thing as if the Applicant had written out each individual substituent of the range, *i.e.*, PTH_{2-84}, PTH_{3-84}, PTH_{4-84}, PTH_{5-84}, PTH_{6-84}, PTH_{7-84}, PTH_{8-84}, an so forth up to PTH_{34-84}.

Moreover, the specification provides specific examples of PTH_{2-84} and PTH_{3-84} (see SEQ ID NOs: 2 & 4), which lie on the N-terminal side of the currently claimed PTH antagonist peptide; and examples of PTH_{9-84}, PTH_{28-84} and PTH_{34-84} (*see* page 1, lines 9-11; page 4, lines 5-6; page 5, lines 23-26; and the sequence listing), which fall within the currently claimed range of a PTH antagonist having an N-terminal position starting at any position spanning from position 8 through position 34 of SEQ ID NO:1 (PTH_{1-84}). Moreover, the present description clearly contemplates PTH antagonists between the range of PTH_{2-84} or PTH_{3-84} and PTH_{34-84}, and between PTH_{8-84} and PTH_{34-}

84. *See id.* Thus, the PTH antagonists are fully supported by the present specification, and are in line with the Court of Customs and Patent Appeals decision *In re Wertheim*, 191 USPQ 90 (CCPA 1976) and MPEP § 2163.05 (range limitations). The Court in *Wertheim* was faced with the question of whether the claimed invention was "part of the invention appellants have described *as theirs* in the specification." *Id.* at 97. Specifically, the question was whether a broadly described range pertains to a different invention than a narrower claimed range. *Id.* at 97-98. In coming to their conclusion, the *Wertheim* court indicated that whether the clams are directed to less than what is described in the specification is "not conclusive" if the specification also reasonable describes what is actually claimed. *Id.* As provided in the MPEP in its description of the *In re Wertheim* decision,

> the ranges described in the original specification included a range of "25% - 60%" and specific examples of "36%" and "50%." A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range, however a limitation to "between 35% and 60%" did meet the description requirement.

MPEP § 2163.05. Admittedly, the present PTH antagonist compositions are not a process for making freeze-dried instant coffee as in *Wertheim*, but the underlying purpose behind the *Wertheim* decision is analogous. The Court in *Wertheim* indicated that claims having the 35-60% limitation were supported by the disclosure, in part, because "persons skilled in the art would consider processes employing a 35-60% solids content range to be part of appellants' invention and would be led by the . . . disclosure so to include." 191 USPQ at 98. *See also Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177 (Fed. Cir. 1985) (The test for sufficiency of support in an application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."). Moreover, the disclosure of the larger range (25%-60%), while having specific examples lying within the subsequently claimed range (35%-60%) (albeit the 35% point was not specifically disclosed in the application but yet became an acceptable lower boundary), clearly evidenced to the Court that the claimed subrange represented the same invention as the larger described range, and was thus a part of the same invention. Similarly, in light of the present disclosure, one of skill in the art would recognize that the current claim to a PTH antagonist having an N-terminal position starting at any position

spanning from position 8 through position 34 of SEQ ID NO:1 (PTH1-84) as adequately supported and part of the same invention described in the specification and claims as originally filed. Accordingly, entry of the present amendment and withdrawal of the New Matter rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 14, 16 and 22-38 stand rejected under 35 U.S.C. § 112, second paragraph as purportedly indefinite. The Office has specifically indicated that claims 14, 22, 26, 30 and 34 remain indefinite "because it is unclear what 'that has the following . . .' in line 7 is intended." The Office has further suggested rewording the claims to overcome the present rejection. The Applicant thanks the office for the suggested claim amendment and herein incorporates the suggestion in claim 14. As claims 22, 26, 30 and 34 are cancelled herein, the present rejection is rendered moot to the extent it previously applied to these claims.

The Office has further indicated that claim 30 remains indefinite "because the claim does not specify the amount being used in the method for decreasing calcium ion concentration in blood in order to achieve said effect set forth in the preamble." The Office has further suggested rewording claim 30 to overcome the present rejection. The Applicant thanks the office for the suggested claim amendment. However, as claim 30 is cancelled herein, this rejection is rendered moot.

It is believed that the presently described amendment to claim 14 merely clarifies certain aspects of the present invention and, as this amendment is not made for reasons related to patentability, it does not narrow the intended scope of the claim.

Rejections Under 35 U.S.C. § 102(b)

Claims 14 and 16 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Takasu *et al.* (Endocrinology, 1996, 137(12): 5537-43) (*Takasu*). The Office has specifically indicated that "Takasu discloses a truncated hPTH mutein, hPTH(35-84), and indicates that it significantly inhibited the [35S] hPTH(1-84) binding." The Office further indicates that one of skill in the art would understand how to construct a pharmaceutical agent from the mutein disclosed in *Takasu*. Notwithstanding the agreement on the issue, out of the concern to provide a complete reply

to the 6 November 2003 Office Action, the Applicant herein places the thrust of his argument on the record for reference by the Office.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). *See also Atlas Powder Co. v. IRECO Inc.*, 51 USPQ2d 1943, 1945-46 (Fed. Cir. 1999) (indicating, in part, that an anticipating reference must include every limitation set forth in the claims); *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1226, 1920 (Fed. Cir. 1989) (every element of the claim must be shown in the reference, including all limitations).

Respectfully, *Takasu* does not disclose every element of the present claims. Moreover, *Takasu's* mutein, as described therein and cited by the office, clearly lies outside of those contemplated in the present claims (and those previously presented). Thus, regardless of the purported activity of *Takasu's* mutein, it does not meet the limitations of the present claims, neither expressly nor inherently. Takasu describes "a truncated hPTH mutein, hPTH(35-84)." Claim 14 is directed to a PTH antagonist having an N-terminal position starting at any position spanning from position 8 through position 34 of SEQ ID NO:1 (PTH1-84), and having a C-terminal position at amino acid residue 84 of SEQ ID NO:1 (PTH_{1-84}). Claim 16 is directed to a PTH antagonist comprising SEQ ID NO:5 (PTH_{28-84}) or SEQ ID NO:3 (PTH_{34-84}). Accordingly, the Applicant respectfully requests withdrawal of this rejection as it applies to claims 14 and 16.

Claims 22-25 and 30-33 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Fukuda, EP 0528271 (*Fukuda*) for reasons set forth in Paper No. 14, pages 4-5. Claims 22-25 and 30-33 are cancelled herein, thus the rejection is rendered moot as it applies to these claims. Moreover, *Fukuda* fails to disclose every element of, and thus does not anticipate, the present claims 39-49.

Fukuda does not teach a method for reducing an anabolic effect of a parathyroid hormone (PTH) on bone in a subject. In contrast, *Fukuda* teaches compositions that have the opposite biological effect compared with the present methods. For example, *Fukuda* provides muteins that

have the same or lower "specific activity" as whole human PTH.[1] *See Fukuda* at page 23, lines 22-42. *Fukuda's* muteins operate through the normal PTH1/PTHrP receptor pathway (*i.e.*, stimulating adenylate cyclase activity), but at a decreased rate to that of regular PTH (*i.e.*, 0.2, 0.3, 0.6, etc., the effect of PTH). Since PTH has an anabolic effect on bone in a subject, *Fukuda's* teaching is that its muteins, though not as potent as PTH, also have an anabolic effect on bone. *Fukuda* does not teach that its muteins can be used to reduce the anabolic effect of PTH on bone. This is in direct contrast to the presently claimed invention, which utilizes specific compositions to reduce the anabolic effect of PTH on bone in a subject. Moreover, as indicated in Figure 2, in the absence of circulating whole PTH, an exemplary composition of the present methods can reduce the calcium ion concentration in the blood of a subject. Thus, the compositions utilized in the present methods function independently of whole PTH and not solely through their inhibitory/competitive effect on the binding of whole PTH with its target receptor. Accordingly, the present claims set forth methods utilizing compositions that could be characterized as agonists with inverse biological activity to that exhibited by PTH. Thus, regardless of what each of these compositions are called, whether it be muteins, agonists, antagonists, etc., *Fukuda* does not teach compositions having the currently claimed biological activity. As the compositions are central components to the presently claimed methods, *Fukuda* cannot anticipate the claimed methods as its compositions are taught as having the opposite activity to those utilized in the present claims. Based on the foregoing, it is clear that *Fukuda* does not teach the methods as currently claimed.

The present rejection is rendered moot by the cancellation of claims 22-25 and 30-33. Nevertheless, based in part on the foregoing, the Applicants respectfully assert that this rejection is not properly applicable to new claims 39-49.

Rejections Under 35 U.S.C. § 103(a)

Claims 26-29 and 34-38 stand rejected under 35 U.S.C. § 103(a) as purportedly rendered obvious by *Fukuda* in view of Kanmera *et al.*, EP 0451867 (*Kanmera*) for reasons set forth in Paper No. 14, pages 5-6. It appears to be the position of the Office that in light of *Kanmera*, one of skill in

[1] *Fukuda's* muteins stimulate adenylate cyclase activity (ACA), as evidenced by the measured mutein-stimulated ACA-linked cAMP levels. *See Fukuda* "Experimental Example" page 23; and Shigeno *et al.* (included herewith and cited in

the art would understand that *Fukuda's* muteins could be utilized to treat the disorders listed in *Kanmera* and would be motivated to do so. Claims 26-29 and 34-38 are cancelled herein, thus the rejection is rendered moot as it applies to these claims. Moreover, the Applicants respectfully assert that new claims 39-49 are not obvious over *Fukuda* in light of *Kanmera*.

First of all, the combination of *Kanmera* with *Fukuda* fails to fill in the holes of the *Fukuda* disclosure (described above) with respect to the present claims. Together these disclosures do not teach methods utilizing compositions that reduce the anabolic effect of PTH on bone in a subject.

Moreover, as indicated by the Federal Circuit:

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. . . . Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 USPQ 1438, 1442 (Fed. Cir. 1991).

The Applicants noted in the response of 30 July 2003 that *Kanmera* describes PTH-related peptide (PTHrP) derivatives rather than PTH peptides. PTHrP is a polypeptide comprised of a different amino acid sequence than PTH, having 141 amino acids rather than the 84 amino acids that comprise human PTH. *Kanmera* suggests altering these PTHrP peptides to attain "potent" "PTH antagonists." Thus, a different class of peptides having different limitations are set forth in *Kanmera* than are provided in the present claims. There is no indication that *Kanmera's* PTHrP derivatives operate via the same biological mechanism as *Fukuda's* muteins, only that the PTHrP derivatives may be "PTH antagonists," whatever meaning is attributed to this term by *Fukuda* and/or *Kanmera*. Although no experimental results are provided, *Kanmera* seems to contemplate the use of the described PTHrP derivatives for treating one or more disorders supposedly involving normal PTH or PTHrP pathways. Importantly, *Kanmera* indicates that PTH and PTHrP fragments

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the *Fukuda* Example).

that lack several amino acid residues at the amino terminal are not desired because they lack practical utility due to low "antagonistic activity" levels. *See, e.g.*, *Kanmera* page 2, lines 47-50. Moreover, *Kanmera* indicates that although peptides having substitutions are desired, such substitutions result in unpredictable activity. *See id.* at lines 50-55. In concluding the buildup to the invention, *Kanmera* indicates that the PTHrP derivatives specifically exemplified therein (by reference to formula (I)) supposedly exhibit the desired activity levels rather than the "vast amount" of PTHrP derivatives that were allegedly examined. *See id.* at lines 56-58.

Kanmera does not cure the deficiencies in *Fukuda* (described above) with respect to the pending claims. Together these references do not teach the use of the presently claimed methods that utilize specific peptide compositions to treat renal osteodystrophy and osteoporosis. Rather, together these references appear to teach that substituted PTH and PTHrP peptides may have enhanced "antagonistic" activity versus that of truncated forms of the peptides and that these substituted peptides may be useful to treat some specific PTH-related disorders as they have lower "activity" levels compared with normal PTH. Solely for the purposes of this argument, based on the teachings of *Kanmera*, one might be motivated to make use of the PTH muteins having an altered (substituted, modified, etc.) PTHrP sequence as an "antagonist" composition, as *Kanmera* seems to teach away from the use of unaltered peptides having merely amino acid residues missing on the N-terminal end. For example, the indication in *Kanmera* that truncated forms of PTH and PTHrP do not have the desired activity levels seems to teach away from the methods of the present claims. And, as the Office is aware, "[r]eferences that teach away cannot serve to create a prima facie case of obviousness." *McGinley v. Franklin Sports, Inc.*, 60 USPQ2d 1001, 1010 (Fed. Cir. 2001). *Kanmera* also appears to teach that substituted forms of PTHrP are utilized rather than truncated PTH or PTHrP, as the latter of these apparently have significantly lower PTH related activity. Notably, *Fukuda* appears to teach substituted/altered PTH muteins. Thus, assuming *arguendo* that the combination of *Fukuda* and *Kanmera* were feasible with a reasonable expectation of success (see below), the combination would utilize *Fukuda's* substituted muteins, or such a combination would run contrary to the teachings of *Kanmera*. Accordingly, the combination asserted by the Office would not suggest the present claims to one of skill in the art.

The supposed motivation to combine *Fukuda* with *Kanmera* (if present at all) is buffered by the precaution issued by *Kanmera* that alterations in the peptide sequence yield unpredictable activity. Accordingly, without the use of *Kanmera's* specifically exemplified PTHrP derivatives, one could not reasonably expect that the "other" peptide compositions of *Fukuda* combined with the *Kanmera* disclosure would be useful to treat the disorders listed in *Kanmera*. Further, in light of the teaching that truncated forms of PTH and PTHrP peptides are not suitable for practical use in *Kanmera* (*see, e.g.*, *Kanmera* page 2, lines 47-50), one of skill in the art would not reasonably expect success in the combination of selected teachings of *Fukuda* and *Kanmera* to deprecate the invention as currently claimed by the Applicant. In other words, based on the foregoing, one would not have a reasonable expectation of success in practicing the claimed methods in light of *Fukuda* together with *Kanmera*. Accordingly, assuming *arguendo* that sufficient motivation were provided to combine *Kanmera* and *Fukuda*, their combined disclosures are insufficient to render the present claims obvious.

The present rejection is rendered moot by the cancellation of claims 26-29 and 34-38. Nevertheless, based in part on the foregoing, the Applicants respectfully assert that this rejection is not properly applicable to new claims 39-49.

CONCLUSION

The Applicant understands that amendments after final are discretionary; however, entry of the amendment and passing the application to allowance (as there appears to be no remaining issues) appears more straightforward and more efficient than resolving these matters on appeal. Accordingly, the consideration of the Office of these amendments is respectfully requested.

If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.532212000300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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